REMARKS

I. Status Of The Claims.

With this Response and Amendment Claims 1-15, 18, and 20-36 are pending. Claims 1, 12, 20, and 26-27 are amended, and new Claims 30-36 are added. Claims 1-4, 9-11, and 18 are rejected under 35 U.S.C. § 102(b), and Claims 1-15, 18, and 20-29 are rejected under 35 U.S.C. § 103(a).

II. Claim Amendments and New Claims.

The amendments to Claims 1, 12, 20, and 26-27 do not add new matter as described below. Entry of these amendments is respectfully requested.

Claim 1.

The amendment to Claim 1 adds the phrase, the biological molecule "being a macromolecule". The term "macromolecule" is already present in Claim 28. Examples of biological molecules that are macromolecules are provided in the specification, such as nucleic acids, including oligonucleotides, DNA, and RNA; carbohydrates; and polypeptides such as proteins and antibodies. This amendment clarifies that Applicants' invention, as limited in Claim 1 to "nucleic acids, polypeptide chains, and carbohydrates" and described in the specification, is directed to "macromolecules". Accordingly, this amendment does not add new matter.

Claim 12.

Claim 12 is amended to add the phrase "providing a biological molecule having at least one reactive amino, thiol, or hydroxyl group, the biological molecule being a macromolecule". This amendment clarifies Applicants' invention and does not add new matter.

Claims 20 and 26-27.

The amendment to Claims 20 and 26-27 adds the phrase, the biological molecule "being a macromolecule". This amendment clarifies Applicants' invention and does not add new matter.

New Claims 30-36.

New Claims 30-36 are based on the specification, *See, e.g.*, pages 2-3; and 4-5 and do not add new matter.

III. The 35 USC § 102 Rejection.

Claims 1-4, 9-11, and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stolowitz et al (WO 87/06586) for the reasons stated in numbered paragraph 2 of the Office Action. Independent Claim 1 is limited to a biological molecule being a "biological macromolecule". The claimed biological macromolecules are not described in Stolowitz et al. Accordingly, Applicants request withdrawal of the rejection under 35 U.S.C. § 102(b) of Claim 1, and Claims 2-4, 9-11, and 18, depending from Claim 1.

IV. The 35 USC § 103 Rejections.

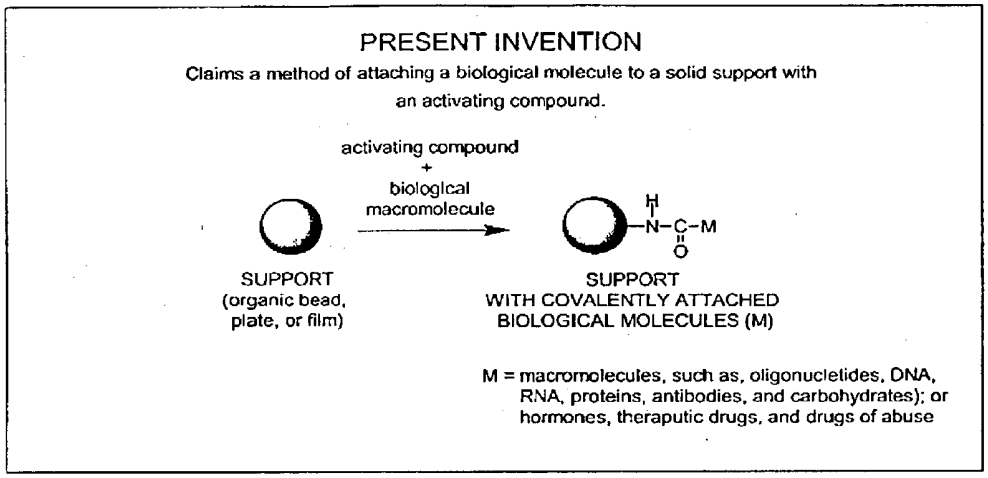
Claims 1-6, 9-15, 18, 20-23, and 25-28 are rejected under 35 U.S.C. § 103(a) as unpatentable over Stolowitz et al. (WO 87/06586) and Milton (US 6,143,833) for the reasons stated in numbered paragraph 5 of the Office Action. Claims 1-15, 18, and 20-28 are rejected under 35 U.S.C. § 103(a) as unpatentable over Stolowitz et al. (WO 87/06586) and Milton (US 6,143,833) and Okamoto et al. (US 6,476,215) and Guo et al. (Nuc. Acids Res. 1994, pp. 5456-5465) for the reasons stated in numbered paragraph 6 of the Office Action. Claims 1-15, 18, and 20-29 are rejected under 35 U.S.C. § 103(a) as unpatentable over Stolowitz et al. (WO 87/06586) and Milton (US 6,143,833) and Okamoto et al. (US 6,476,215) and Guo et al. (Nuc. Acids Res. 1994, pp. 5456-5465) and Ekins et al. (Ekins, R. and Chu, F. "Microarrays: their origins and applications" TIBTECH June 1999, 17, 217-218) for the reasons stated in numbered paragraph 10 of the Office action.

Applicants respectfully traverse these bases for rejection on the basis that no *prima facie* case of obviousness has been established. Applicants request reconsideration based on the following remarks, withdrawal of the rejection, and allowance of all Claims

A. The Claimed Invention.

The invention is directed to a method for attaching biological molecules to a solid support. The invention solves the disadvantages of the prior art, such as those disclosed in Milton, U.S. No. 6,143,833, by reducing the number of steps necessary to covalently attach a biological molecule to a solid support, and increasing the loading of biological molecules onto the solid support for synthesis and analyte detection. (*See, e.g.*, Specification, page 1). The advantages of the claimed invention over the prior art are that it is more efficient, economical,

simpler and faster, with greater sensitivity. As shown in the figure below, the invention solves the prior art problems of attaching biological molecules by requiring the combination of a solid support with an available amino group, and an activating group, which attaches both the solid support and the biological molecule.



B. The Rejection over Stolowitz et al. and Milton.

1. Claims 1-15, 18, and 20-28.

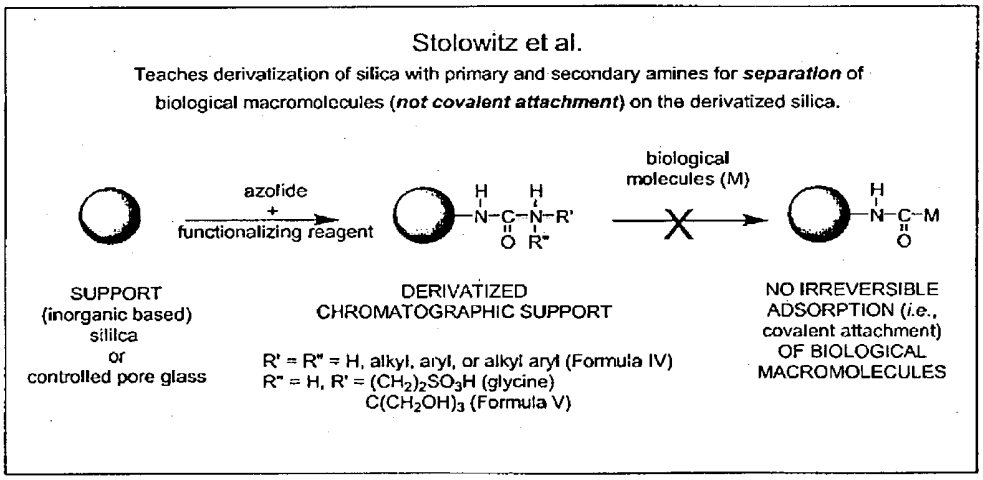
Claims 1-6, 9-15, 18, 20-23, and 25-28 are rejected under 35 U.S.C. § 103(a) as unpatentable over Stolowitz et al. and Milton for the reasons stated in numbered paragraph 5 of the Office Action. Applicants respectfully traverse this rejection on the basis that the Office has not established a *prima facie* case of obviousness as there is no motivation to modify or combine the references.

Stolowitz et al. does not describe the limitation of pending Claims 1-15, 18, and 20-28 of covalent attachment of a biological macromolecule to a solid support using the claimed activating compound. The Office looks to combine the teachings of Milton to remedy the deficiencies of Stolowitz. However, Stolowitz et al. teaches *separation* of the claimed biological molecules, and expressly teaches against covalent attachment of the claimed biological molecules. The proposed combination of Stolowitz et al. and Milton is completely contrary to the teaching of Stolowitz et al. If Stolowitz et al. is combined with Milton,

Stolowitz et al. would not work for its intended purpose. No person of ordinary skill in the art would make the combination, and thus a *prima facie* case of obviousness has not been established.

Independent Claims 1, 12, 20, and 26-28 and their dependent claims, are each limited to a "biological molecule being a macromolecule" and "reacting the biological molecule with the activated support, thereby displacing L_2 and **covalently** attaching the biological molecule to the solid support." (emphasis added), in varying language. These limitations are not described in Stolowitz et al.

Further, Stolowitz et al. teaches derivatized silica and porous glass beads for chromatographic *separation* of biological macromolecules and low molecular weight amines (*i.e.*, biomolecules). As known to those of skill in the art and taught on page 2, lines 1-13; and page 4, lines 1-9 of Stolowitz, for the chromatographic support to suitably function, it is desirable that the chromatographic support does not irreversibly absorb (*i.e.*, covalently attach) the biomolecules. The teachings of Stolowitz et al. are illustrated in the figure below.



Attaching the claimed biological macromolecules, such as oligonucleotides, as taught by Milton, is directly against the teachings of Stolowitz et al., which expressly teaches no irreversible adsorption (*i.e.*, covalent attachment) of these molecules.

Milton also does not provide the requisite motivation to modify or combine the references to arrive at Applicants claimed invention. Milton's disclosure of a solid support

having a pendant acyl fluoride functionality for immobilizing biopolymers does not teach or suggest Applicants' claimed amine derivatized supports or activating compound. Milton discloses immobilizing biopolymers with entirely different attachment chemistry than the attachment chemistry claimed by Applicants. There is absolutely no suggestion of the desirability of combining the attachment chemistry of Stolowitz et al. with the disclosure in Milton of immobilizing biopolymers, especially in view that Stolowitz et al. teaches the derivatized solid supports which "eliminates the irreversible adsorption of biological macromolecules" (Stolowitz et al. page 4, lines 6-7).

As detailed above, there is no suggestion or motivation to modify or combine the references to arrive at Applicants' invention as Stolowitz et al. teaches away from the proposed combination. Accordingly, a *prima facie* case of obviousness has not been established. Applicants request withdrawal of the § 103 rejection over Stolowitz et al. and Milton and allowance of pending Claims 1-15, 18, and 20-28.

2. Claims 12-15 and 20-27.

In addition, to the reasons to the reasons above that Applicants' invention is non-obvious over Stolowitz and Milton, neither Stolowitz et al. nor Milton, alone or in combination, describe the limitation of independent Claims 12, 20, and 26-27, and their dependent claims of the various claimed solid supports having at least one available amino group.

Claims 12 and 14-15 are limited to "providing a solid support having at least one available amino group, the solid support selected from the group consisting of a plate and a film". Claims 20-25 and 27 are limited to "providing a solid support having at least one available amino group, the solid support being formed from a material selected from the group consisting of cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon." Claim 26 is limited to "providing a solid support comprised of an organic polymer having at least one available amino group".

As admitted by the Office, Stolowitz et al. does not teach these claimed limitations (See, Office Action, page 5, line 18 through page 6, line 3). Milton does not remedy the deficiencies of Stolowitz et al. as Milton does not teach or suggest amine derivatized solid

supports. Specifically, Milton does not teach or suggest:

(1) amine derivatized plates and films (Claims 12-15);

(2) amine derivatized solid supports formed from cellulose, agarose, polypropylene, polystyrene, polymethacrylate, and nylon (Claims 20-25 and 27); and

(3) amine derivatized organic polymers (Claim 26).

Further, one of ordinary skill in the art would not be motivated to modify or combine Stolowitz et al. and Milton, as Milton teaches the desirability of solid supports having acyl fluoride functionalities. There is no suggestion in Milton that solid supports "having at least one amino group" is desirable to attach a biological molecule, and as previously discussed, Stolowitz directly teaches against attaching biological molecules.

Milton also teaches that prior art derivatized "glass slides, silicon wafers and polymer films" are difficult to handle and require special handles or holders that are expensive to manipulate the solid support (Col. 2, lines 5-27). Milton then teaches that solid supports fabricated with acyl fluoride functionalities overcome the disadvantages of the prior art. (Col. 3, lines 53-66).

As detailed above, (i) the combination of Stolowitz and Milton does not describe Applicants claimed amine derivatized solid supports; and (ii) there is no suggestion or motivation to modify the references to arrive at Applicants claimed invention. Thus, Applicants request withdrawal of the rejection and allowance of Claims 12-15 and 25-27 on the basis that the Office has not established a *prima facie* case of obviousness.

C. The Rejection over Stolowitz et al. and Milton and Okamoto et al. and Guo et al.

Claims 1-15, 18, and 20-28 are rejected under 35 U.S.C. § 103(a) as unpatentable over Stolowitz et al. and Milton and Okamoto et al. and Guo et al. for the reasons stated in numbered paragraph 6 of the Office Action. Applicants traverse this rejection on the basis that the Office has not established a *prima facie* case of obviousness.

1. Claims 1-15, 18, and 20-28.

Claims 1-15, 18, and 20-28 are non-obvious over Stolowitz et al. and Milton, for the reasons detailed in section IV(B) above. As detailed in section IV(B) above, Stolowitz et al.

does not describe (i) covalent attachment of biological macromolecules to a solid support using the claimed activating compound and there is no motivation to modify or combine Stolowitz et al. and Milton as Stolowitz et al teaches the undesirability of covalent attachment of the claimed biological macromolecules (Claims 1-15, 18, and 20-28); and (ii) the combination of Stolowitz et al. and Milton does not describe Applicants claimed amine derivatized solid supports (Claims 12-15 and 20-27).

Combining Okamoto et al. and Guo et al. does not remedy the deficiencies of Stolowitz et al. and Milton. There is no description in either Okamoto et al. or Guo et al. of (i) "reacting the available amino group on the solid support with an activating compound" of Applicants claimed formula "L_1 - X- L_2", or (ii) "reacting the biological molecule with the activated support, thereby displacing L_2 and covalently attaching the biological molecule to the solid support", limitations of all pending claims. Guo et al. teaches modifying the solid support with phenyleneisothiocyanate. (*See, e.g.*, Figure 1, page 5458). Okamoto et al. teaches maleimido modifed solid supports. There is no description in either Okamoto et al. or Guo et al. of "displacing L_2 and covalently attaching the biological molecule to the solid support." The attachment chemistry described in Okamoto et al. and Guo et al. is mechanistically different than Applicants claimed invention and there is no teaching or suggestion of Applicants invention which is limited to "displacing L_2 and covalently attaching the biological molecule to the solid support".

Accordingly, one of ordinary skill in the art would not be motivated to modify or combine Stolowitz et al., and Milton, and Okamoto et al. and Guo et al. as:

(i) Neither Okamoto et al. nor Guo et al. alone or in combination suggests covalent attachment of biological macromolecules to a solid support using Applicants' claimed activating compound;

(ii) Milton teaches the desirability of solid supports having acyl fluoride functionalities and there is no suggestion in Milton of solid supports "having at least one amino group", or "reacting the available amino group on the solid support with an activating compound"; and

(iii) Stolowitz directly teaches against covalently attaching biological macromolecules.

Accordingly, a *prima facie* case of obviousness has not been established. Applicants

request withdrawal of the § 103 rejection over Stolowitz et al. and Milton and Okamoto et al. and Guo et al. and allowance of pending Claims 1-15, 18, and 20-28.

2. Claims 20-27.

In addition to the reasons stated above that Applicants invention is non-obvious over Stolowitz et al. and Milton and Okamoto et al. and Guo et al., neither Stolowitz et al., Milton, Okamoto et al., nor Guo et al. teach all the limitations of Claims 20-27. The Examiner has not cited ***any*** solid support "having at least one available amino group" which is "a cellulose, an agarose, a polypropylene, a polystyrene, a polymethacrylate, and a nylon" (Claims 20-25 and 27); and "an organic polymer" (Claim 26). There is no teaching in Milton of amino derivatized solid supports and Milton teaches the desirability of acyl fluoride derivatized solid supports. Stolowitz et al., and Okamoto et al., and Guo et al. also do not teach these claimed solid supports.

Applicants additionally request withdrawal of the § 103 rejection of Claims 20-27 over Stolowitz et al. and Milton and Okamoto et al. and Guo et al. on this basis.

D. The Rejection over Stolowitz et al. and Milton and Okamoto et al. and Guo et al. and Ekins et al.

Claims 1-15, 18, and 20-29 are rejected under 35 USC § 103(a) over Stolowitz et al. and Milton and Okamoto et al. and Guo et al. and Ekins et al. for the reasons stated in numbered paragraph 10 of the Office Action. Claims 1-15, 18, and 20-29 are non-obvious over Stolowitz et al. and Milton and Okamoto et al. and Guo et al. for the reasons stated in sections IV(B) and IV(C) above.

For Claim 29, the Office admits that the combined teachings of Stolowitz et al. and Milton and Okamoto et al. and Guo et al. do not teach "hormones, therapeutic drugs, or drugs of abuse." However, the Office has not established a *prima facie* case of obviousness by combining the teachings of Ekins et al. with the teachings of Stolowitz et al. and Milton and Okamoto et al. and Guo et al. as follows:

(i) The combination of Milton, Okamoto et al., Guo et al. and Ekins et al. does not teach or suggest "reacting the available amino group on the solid support with an activating compound" of Applicants' claimed formula "L_1 - X- L_2", or "displacing L_2 and covalently

attaching the biological molecule to the solid support"; and

(ii) Stolowitz teaches away from the proposed combination. Stolowitz et al. teaches derivatized silica and porous glass beads for chromatographic separation (not covalent attachment) of biological molecules, such as hormones, therapeutic drugs, or drugs of abuse. (*e.g.*, Stolowitz et al., page 4, lines 1-9, describes that the invention "eliminates the irreversible adsorption of biological macromolecules and low molecular weight amines).

Accordingly, a *prima facie* case of obviousness has not been established. Applicants request withdrawal of the § 103 rejection over Stolowitz et al. and Milton and Okamoto et al. and Guo et al. and Ekins et al. and allowance of all pending Claims.

CONCLUSION

The Applicant believes that all pending claims are in condition for allowance and such action is earnestly requested. If the present amendments and remarks do not place the Application in condition for allowance, the Examiner is encouraged to contact the undersigned directly if there are any issues that can be resolved by telephone with the Applicants representative.

The Commissioner is authorized to charge $194 for the excess claim fees. No other fees are believed due by this Response. If, however, any other fees are due, the Commissioner is authorized to charge any other fees associated with this Response and Amendment to Deposit Account No. 19-2090.

Respectfully Submitted,
SHELDON & MAK PC

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